DRAIHA study

Data Registry of AutoImmune Hemolytic Anemia, to improve diagnostic testing for the development of personalized treatment protocols in AIHA patients

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RESEARCH | DIAGNOSTICS | PHARMACEUTICALS

LUMC

Disclosure belangen spreker bijeenkomst Consortium Transfusiegeneeskundig Onderzoek 02-11-2018	
Naam: Marit Jalink	
Geen (potentiële) belangenverstrengeling	**Geen**
Voor bijeenkomst mogelijk relevante relaties	**Geen**
• **Sponsoring of onderzoeksgeld** • **Honorarium of andere (financiële) vergoeding**	· **Sanquin PPOC** · · ·

AutoImmune Hemolytic Anemia (AIHA)

Estimated incidence: 1-3 per 100.000 persons/year

| AIHA serological type	N (%)
Warm, DAT+ IgG	131 (43%)
Warm, DAT+ IgG/C3d (IgM)	52 (17%)
CAD, DAT+ C3d (plus CA with a-I) (IgM)	84 (27%)
Mixed, DAT+ IgG/C3d, WA plus CA	24 (8%)
Atypical, DAT neg, + for IgA, warm IgM	16 (5%)

Barcellini et al. 2014
Meulenbroek et al. 2015

Diagnosis AIHA

General laboratory findings:

- Hemolysis (LDH ↑, haptoglobulin ↓, hyperbilirubinaemia ↑, haemoglobinuria, reticulocytosis)
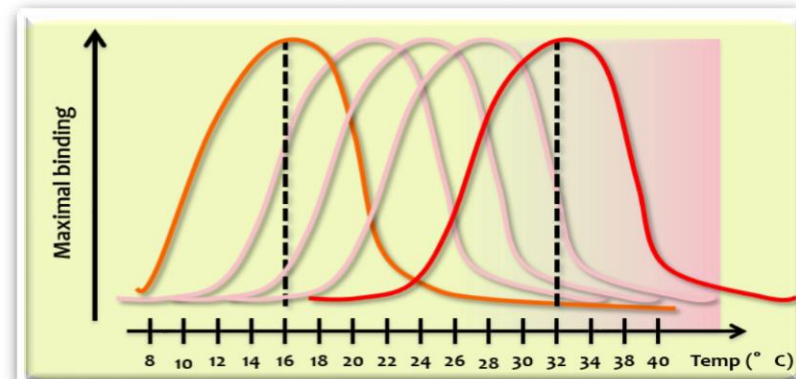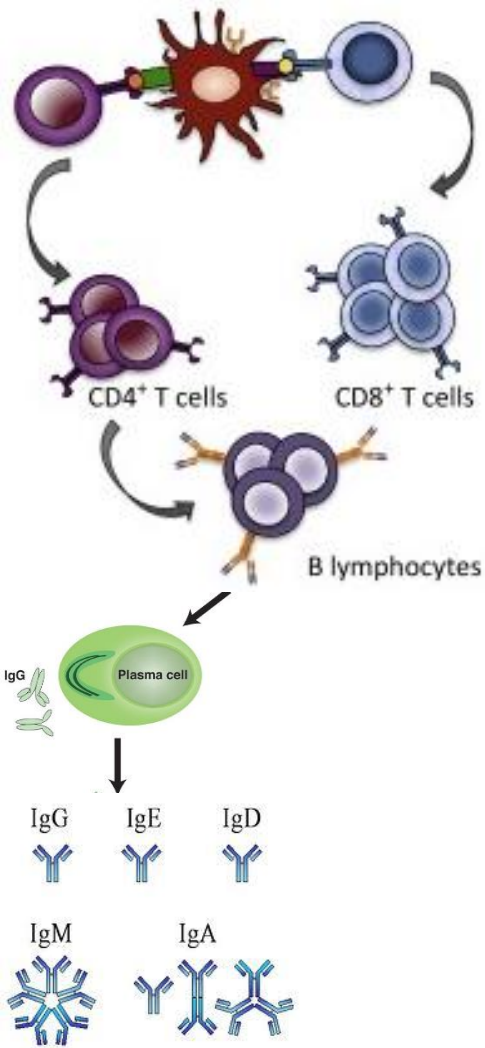- Positive Coombs ~ DC ~ direct antiglobulin test (DAT)

Pitfalls in the diagnosis:

- ~ 8% false positive DAT in hospitalized patients
- ~ 10% false negative DAT
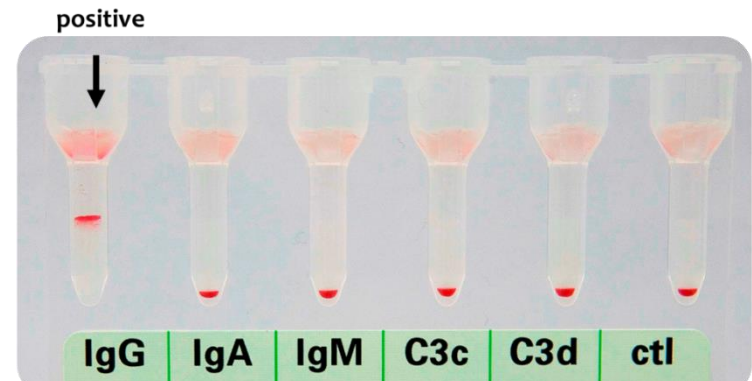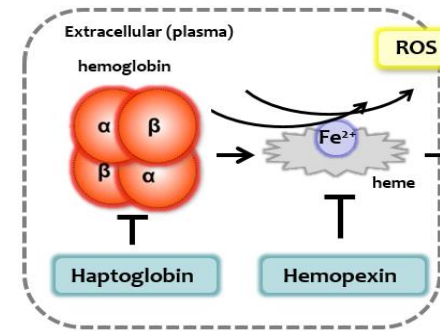
AIHA- Clinical significance autoantibody

1. Isotype and subclass

2. Thermal amplitude

3. Efficiency in activation complement
- In- or extravascular hemolysis

4. Specificity autoantibody:
- Rh, Kell of glycophorines, Band3
- I/i (AIHA cold antibody)
- P (paroxsysmal cold hemoglobinuria)

Dysregulation immune system

Systemic inflammation
Tissue damage

CD4+ T cells

CD8+ T cells

B lymphocytes

IgG

Plasma cell

IgG   IgE   IgD

IgM   IgA

Extracellular (plasma)

hemoglobin

ROS

α   β

β   α

Fe²⁺

heme

Haptoglobin

Hemopexin

Antibody properties
e.g. quantity, affinity, Fc properties, specificity, clearance induction

Extravascular
hemolysis

C3

Intravascular
hemolysis
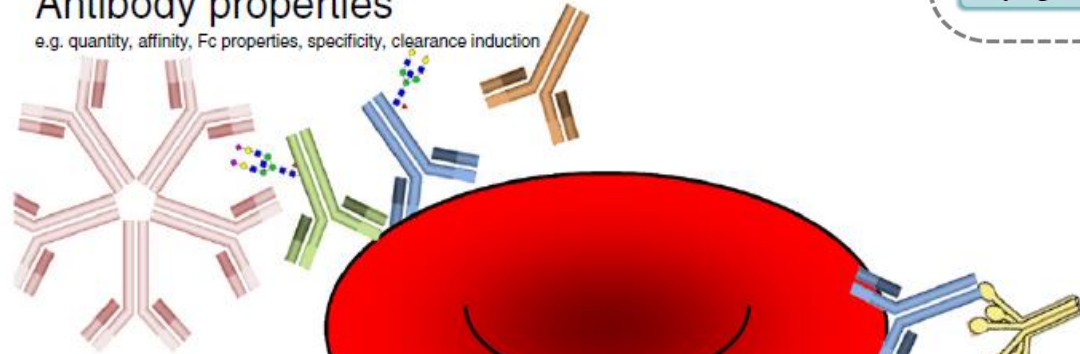
Clearance system properties
e.g. Fcγ-receptor polymorphisms, activity phagocytes, involvement other
immune cells, levels of complement regulators

Phagocyte
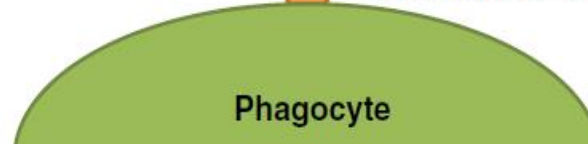
Missing knowledge

1. Optimal diagnostics for "Personalised Medicine"
   - Detect new pathogenic pathways for targeted therapy
     - Pathogenic effect of antibodies
     - Immune dysregulation (T or B cell dysregulation)

2. Optimal red blood cell selection for transfusion
   - Minimalize the risk of aggravation of hemolysis

3. The predictive value of a positive DAT in patients and donors

Blood donors with positive direct antiglobulin tests are at increased risk for cancer.

Rottenberg Y[1], Yahalom V, Shinar E, Barchana M, Adler B, Paltiel O.

Case Report

DAT positivity in blood donors: A perplexing scenario

Ravneet Kaur Bedi *, Kshitija Mittal [1], Tanvi Sood [1], Rakesh Kumar [1], Ajay S. Praveen

Department of Transfusion Medicine, Government Medical College and Hospital, Sector 32, Chandigarh, India

Management of blood donors and blood donations from individuals found to have a positive direct antiglobulin test.

Hannon JL[1].

Incidence of clinically significant antibodies in patients and healthy blood donors: A prospective cross-sectional study from a tertiary healthcare center in India

Aseem K. Tiwari [a] ⚇ ✉, Prashant Pandey [a], Jyoti Sharma [a], Kumari Shailja [b], Surbhi Dixit [a], Vimarsh Raina [c]

DRAIHA study

- An observational (multicenter) cohort study

- **Inclusion criteria:**
  - Patients (> 3 months old):
      DAT+ with positive eluate
      DAT+ with complement and with hemolysis

  - Blood donors: DAT+ with positive eluate or clinical relevant cold autoantibodies

DRAIHA study – design

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Exclusion:

Refuse to participate or no informed consent

Eligible for DRAIHA study:

1. Patients with a positive DAT and a positive eluate
2. Patients with a positive DAT with complement only, negative eluate, but with hemolysis

← ↓

At time of inclusion:

1. Clinical data (questionnaire patient/blood donor and (donor-) physician)
2. Standard set of diagnostic assays
3. Set of experimental diagnostic assays

↓

After 1-2 year of follow up:

1. Clinical data (questionnaire patient/blood donor and (donor-) physician)
2. Standard set of diagnostic assays
3. Set of experimental diagnostic assays

↓

Evaluation of diagnostic test results in correlation with clinical data (transfusion, medical treatment and outcome).

↓

Primary endpoint

Determine diagnostic predictors for the course of AIHA.

Secondary endpoints

1. Determine diagnostic predictors for safe and efficient blood transfusion in AIHA patients.
2. Develop a clinical guideline for follow-up and counselling of direct antiglobulin test (DAT)-positive blood donors.

Primary objective:

- Determine diagnostic predictors for the clinical course in AIHA patients

  → Is the specification of a positive direct antiglobulin test and/or red blood cell autoantibody specification correlated with the clinical course in patients with AIHA

Secondary objectives:

- Determine diagnostic predictors for safe and efficient blood transfusion in AIHA patients.

- Determine the clinical consequences of DAT-positivity in blood donors to develop a clinical guideline for follow up and counseling.
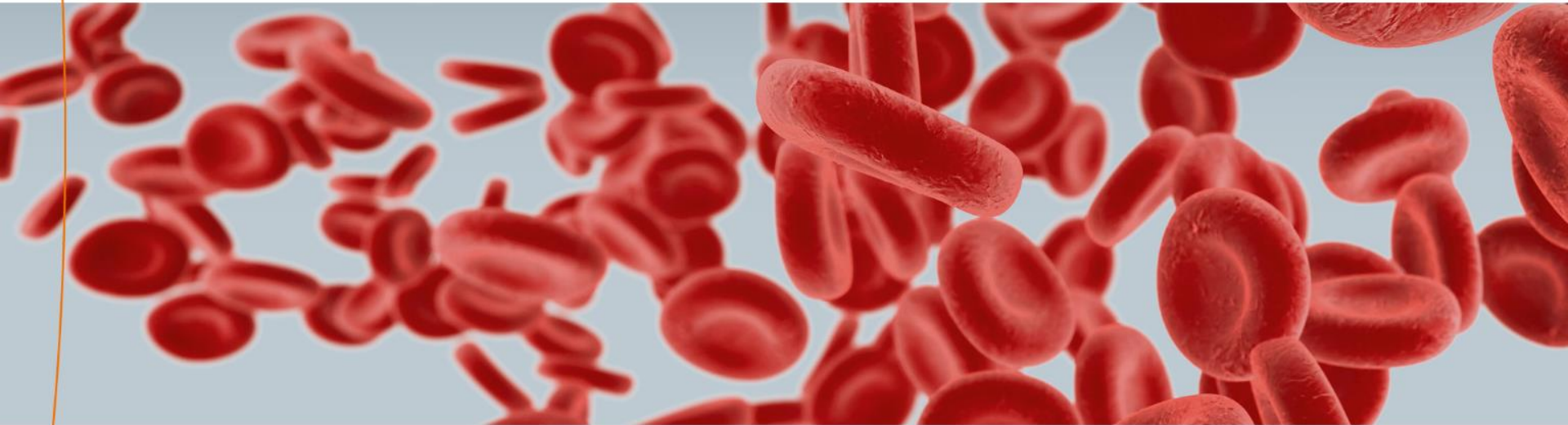
Pathophysiology-
research objectives

- **Autoantibody characteristics** : isotype and Fc polymorfisme, specificity, affinity, complement activation, 'thermal amplitude', variation in glycosylation, interaction with phagocytes.

- **Antigen characteristics:** expression (glyco-)proteïns on the RBC, loss of antigens.

- **Complement** mediated cellysis

- **Variation in clearance:** Fc-receptor polymorfism, phagocyte activity, membrane bound complement regulators.

- **Dysregulation of the immunesystem**: B- and T-cell subsets

- **Systemic inflammation** and **cytokine profiles**

- **Genetic risk analysis, molecular typing**